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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/186,869	11/04/98	HASEL	K 98.429

HM22/1025
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EXAMINER	
FREDMAN, J	
ART UNIT	**PAPER NUMBER**
1655	19

DATE MAILED: 10/25/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/186,869	Applicant(s) Hasel et al
	Examiner Jeffrey Fredman	Group Art Unit 1655

☒ Responsive to communication(s) filed on *Aug 23, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-74* is/are pending in the application.

Of the above, claim(s) *37-41, 73, and 74* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-36 and 42-72* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *9, 12*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I in Paper No. 18 is acknowledged. The traversal is on the ground(s) that the inventions are linked by an underlying technical feature. This argument, which appears to be addressed to the distinctiveness of the inventions, is not found persuasive because each invention has separate utilities as discussed in the restriction requirement and evidence of such distinctness is present in the separate classification. The current requirement is not a lack of unity, but rather a restriction requirement, which only requires distinctness and burden. The separate classification also serves as prima facie evidence of a search burden, which is not rebutted.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 8, 10-36 and 42-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Erlander et al (WO 95/13369) in view of New England Biolabs catalog (page 11) (1993/1994 catalog).

Erlander teaches an improved method for the simultaneous sequence-specific identification of mRNAs in a mRNA population comprising:

(a) preparing double-stranded cDNAs from a mRNA population optionally enriched for Poly A sequences (page 20, lines 8-13) using mixture of 12 anchor primers, the anchor primers each including: (i) a tract of from 7 to 40 T residues; (ii) a site for cleavage by a restriction endonuclease that recognizes more than six bases, the site for cleavage being located to the 5'-side of the tract of T residues; (iii) a stuffer segment of from 4 to 40 nucleotides, the stuffer segment being located to the 5'-side of the site for cleavage by the restriction endonuclease; and (iv) phasing residues -V-N located at the 3' end of each of the anchor primers, wherein V is a deoxyribonucleotide selected from the group consisting of A, C, and G; and N is a deoxyribonucleotide selected from the group consisting of A, C, G, and T, the mixture including anchor primers containing all possibilities for V and N (page 8, lines 18-36),

(b) cleaving the double stranded cDNA population with a two restriction endonucleases, one of which recognizes four nucleotide sequences and one of which cleaves within the anchor region (page 9, lines 1-11),

(c) inserting the double stranded cleaved cDNA from step (b) into a vector in an orientation that is antisense with respect to a bacteriophage-specific promoter within the vector, (page 9, lines 1-11), expressly teaching the use of the pBC SK vector in which the NotI restriction site is more than 15 nucleotides in length from the transcription initiation site of either T3 or T7 (page 22, lines 16-26),

(d) transforming the host cell with the vector in which the cleaved DNA has been inserted to produced vectors containing cloned inserts (page 9, lines 1-11 and page 22, lines 28-36),

(e) generating linearized fragments of the cloned inserts by digestion with at least one restriction endonuclease that is different from the first and second restriction endonucleases but which cleaves within the vector (page 9, lines 12-15 and page 23, line 9 to page 24, line15),

(f) generating a cRNA preparation of antisense cRNA transcripts by incubation of the linearized fragments with a bacteriophage-specific RNA polymerase capable of initiating transcription from the bacteriophage-specific promoter (page 9, lines 16-20),

(g) generating a first strand cDNA by transcribing the cRNA using reverse transcriptase and by dividing the cRNA preparation into sixteen subpools and transcribing first-strand cDNA from each subpool, using a thermostable reverse transcriptase and one of sixteen primers whose 3'-terminus is -N-N, wherein N is one of the four deoxyribonucleotides A, C, G, or T, the primer

being at least 15 nucleotides in length, corresponding in sequence to the 3'-end of the bacteriophage-specific promoter, and extending across into at least the first two nucleotides of the cRNA, the mixture including all possibilities for the 3'-terminal two nucleotides; (page 9, lines 21-31),

(h) generating a first set of PCR products by using the product of transcription in each of the sixteen subpools as a template for a polymerase chain reaction with a 3'-primer that corresponds in sequence to a sequence in the vector adjoining the site of insertion of the cDNA sample in the vector and a 5'-primer selected from the group consisting of: (i) the primer from which first-strand cDNA was made for that subpool; (ii) the primer from which the first-strand cDNA was made for that subpool extended at its 3'-terminus by an additional residue -N, where N can be any of A, C, G, or T; and (iii) the primer used for the synthesis of first-strand cDNA for that subpool extended at its 3'-terminus by two additional residues -N-N, wherein N can be any of A, C, G, or T, to produce polymerase chain reaction amplified fragments; (page 9, line 32 to page 10, line 10),

(j) resolving the polymerase chain reaction amplified fragments by electrophoresis to display bands representing the 3'-ends of mRNAs present in the sample (page 10, lines 11-13).

Erlander teaches anchor primers with 18 T residues in the T tract (page 16, line 13). Erlander further teaches stuffers anywhere in the range of 4-40. Erlander expressly teaches the use of the T3 promoter (page 24, lines 16-27).

Erlander expressly teaches associating changes in expression with physiological or pathophysiological change using wildtype and test samples (pages 29-33), including processes mediated by growth factors such as steroids (page 33, line 5), tissues such as CNS tissue (page 31, line 4), or retina (page 30, line 25), or peripheral nervous system (page 31, line 20), skeletal muscle (page 31, line 24) diseases such as Alzheimers (page 30, line 31), or glutamate neurotoxicity (page 31, line 7), aging or long-term potentiation (page 31, line 1).

Erlander expressly teaches using the method to determine the effect of drugs being screened (page 31, lines 11-15) including antidepressants (page 32, line 34), steroids (page 33, line 5).

Erlander expressly teaches correlating relative abundance of mRNA with the signal produced including the use of fluorescent labels (page 38, lines 29-36) as well as a preference for use of one gel, but directly suggests that multiple gel should be used where sample number requires (page 27, lines 13-35).

Erlander further teaches eluting a cDNA from the gel, amplifying the eluted cDNA by PCR, cloning the amplified DNA, producing the DNA and sequencing it (page 33, lines 14-23).

Erlander does not teach, but does expressly suggest, three elements of the claims. Erlander suggests step (i), which is a repetition of step (h). Erlander suggests the use of restriction enzymes but does not name each enzyme claimed. Erlander generically describes the sequences required, but does not identify the specific sequences claimed.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to follow the suggestion of Erlander who expressly suggests repeating step (h), stating "The use of successive steps with lengthening primers to survey the cDNAs essentially act like a nested PCR (page 28, lines 19-21)". Erlander further notes "In serial iterations of the subsequent PCR step, in which radioactive label is incorporated into the products for autoradiographic visualization, those pools are further segregated by division into four or sixteen subpools by using progressively longer 5' primers containing three or four nucleotides of the insert (page 28, line 32 to page 29, line 2)". Erlander therefore expressly suggests phasing up to three or four nucleotides (page 29).

Erlander expressly suggests the use of any restriction enzyme, including any routine equivalent, and expressly discusses a variety of different enzymes on pages 21-23. The examiner takes official notice of the fact that each of the enzymes cited in claims 24-36 are well known in the art enzymes each of which is completely characterized and whose characteristics fall within those taught and required by Erlander and each of which is commercially available in catalogs of restriction enzymes as exemplified by page 11 of the New England biolabs catalog.

With regard to the specific SEQ ID Nos claimed, these sequences appear to simply represent arbitrary selection of sequences. In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (34 USPQ 2d 1210, 1214)."

Since the claimed oligonucleotides simply represent structural and functional homologs of the Erlander sequences, which are sequences which have been identified by the prior art as being useful for indexing method, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

4. Claims 1-4, 8, 10-36 and 42-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Erlander et al (WO 95/13369) in view of New England Biolabs catalog (page 11) (1993/1994 catalog) and further in view of Kato et al (EP 735 144 A1).

Erlander in view of NEB catalog teaches the limitations of claims 1, 8, 10-36 and 42-72 as discussed above. Erlander in view of NEB does not teach the use of biotin, streptavidin for cDNA capture.

Kato teaches the use of biotin and streptavidin coated magnetic beads for capture of labeled nucleic acid indexing amplified molecules (figure 1 and page 4, lines 30-40).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize biotin and streptavidin to separate the nucleic acid products as taught by Kato in the method of Erlander in view of NEB catalog since Kato states "By using a class-II restriction enzyme, a class IIS restriction enzyme and 64 biotinylated adaptors in the operations described above, the DNA or cDNA fragments generated by class II and class IIs restriction enzymes can be separated. (Page 5, lines 53-55)." An ordinary practitioner would have been motivated to use the biotin streptavidin system for isolation of nucleic acids in order to easily separate the components using magnetic beads as taught by Kato, and in particular, to easily separate out the restricted DNA as taught by Kato.

5. Claims 1, 5-7, 8, 10-36 and 42-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Erlander et al (WO 95/13369) in view of New England Biolabs catalog (page 11) (1993/1994 catalog) and further in view of Noronha et al (PCR Methods Appl (1992) 2:131-136).

Erlander in view of NEB catalog teaches the limitations of claims 1, 8, 10-36 and 42-72 as discussed above. Erlander in view of NEB does not teach the use of phosphorothioate linkages.

Noronha teaches the use of phosphorothioate linkages in PCR in order to prevent primer degradation (abstract).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize phosphorothioate linkages as taught by Noronha in the method of Erlander in view of NEB catalog since Noronha states "The data presented here demonstrate

that while 3'-5' exonuclease activity can be a hindrance to efficient specific DNA amplification, its activity can be diverted from amplimer degradation and restricted to proofreading through the use of 3' sulfurized amplification amplimers (page 135, column 3)". An ordinary practitioner would have been motivated to combine the use of phosphorothioate oligonucleotides with the method of Erlander in view of NEB catalog in order to reduce background and amplimer degradation.

6. Claims 1, 8-36 and 42-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Erlander et al (WO 95/13369) in view of New England Biolabs catalog (page 11) (1993/1994 catalog) and further in view of Ju et al (Anal. Biochem. (1995) 231:131-140).

Erlander in view of NEB catalog teaches the limitations of claims 1, 8, 10-36 and 42-72 as discussed above. Erlander in view of NEB does not teach the use of the specific fluorophores claimed.

The specification admits, on page 13, lines 25-30, that these probes are all known in the prior art.

Ju teaches the use of several of these dyes for DNA analysis (abstract).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the fluorescent dyes of Ju in the method of Erlander in view of NEB catalog because Erlander expressly suggests the use of fluorescent dyes and Ju states "The unique spectroscopic properties of ET primers make them valuable in all areas where high sensitivity and simultaneous spectroscopic discrimination of several fluorescent tags is required (page 140, column 1)". An ordinary practitioner would have been motivated to use the

fluorophores of Ju in the method of Erlander in view of NEB catalog for the express motivation of high sensitivity and improved discrimination.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeff Fredman, Ph.D. whose telephone number is (703) 308-6568.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Jeffrey Fredman
Primary Patent Examiner
Art Unit 1655

October 18, 2000